REMARKS/ARGUMENTS

I. Status of the Claims

Claims 14, 19, 20, 25, 55, 56, 72, 75 and 93-116 are pending. A listing of the claims is presented for the Examiner's convenience. No claims have been amended, added or cancelled by this Amendment.

By this Amendment, no new matter has been added to the application.

II. Response to Rejections Under 35 U.S.C. 103(a)

Introduction/Summary of Arguments

Claims 14, 19, 20, 25, 55, 56, 93-98 and 105-108 are rejected as being allegedly obvious over Becker et al., EP 0613 007 ("Becker") and further in view of Audia et al., U.S. Patent No. 5,965,614. ("Audia") and, alternatively, over Becker, further in view of Audia as evidenced by Johnson-Wood, et al., *Proc. Natl. Acad. Sci. USA* (1997) ("Johnson-Wood"). Claims 14, 19, 20, 25, 72, 75, 99-104 and 109-120 are rejected as being allegedly obvious over Becker in view of Mak et al., *Brain Res.*, 1994, 19:138-142 ("Mak").

Applicant has previously responded to the rejections in an Amendment filed July 24, 2009, which sets forth reasons the rejections should be withdrawn, and which is incorporated herein by reference. In further response to the rejections, Applicant submits an accompanying Declaration of Norman R. Relkin, M.D., Ph.D., Under 37 C.F.R. 1.132 (the "Relkin Declaration") which sets forth the reasons one of ordinary skill in the art in April 1997 would not have combined Becker with Audia, Audia and Johnson-Wood, or Mak to arrive at the claimed invention. The Relkin Declaration provides evidence that (i) a person of ordinary skill in the art in April 1997 would not have been motivated to combine Becker with Audia, Johnson-Wood or Mak; (ii) in April 1997 there was no reasonable expectation of success for combining Becker

with Audia and Johnson-Wood or Becker with Mak to treat Alzheimer's disease; and (iii) the stated grounds for the rejections are based on a flawed factual analysis of the scope and content of the prior art.

Based on the evidence provided in the Relkin Declaration, the obviousness rejections should be withdrawn because (1) one of ordinary skill in the art in April 1997 would have had no rationale for combining the prior art of record; (2) in April 1997 there was no reasonable expectation of success for combining the prior art to arrived at the claimed invention; (3) the Examiner has not properly ascertained the scope and content of the prior art that are among the factual findings required to sustain a finding of obvious; and (4) in April 1997 the claimed invention would not have been obvious to try.

No Motivation/Rationale to Combine the Prior Art/No Reasonable Expectation of Success

An obviousness rejection predicated on a combination of prior art references requires that at the time the invention was made there was a rationale or motivation that would have motivated one of ordinary skill in the art to combine the prior art and a reasonable expectation of successfully combining the prior art to arrive at the claimed invention. *In re Dow Chem. Co.,* 837 F.2d 469, 473 (Fed. Cir. 1988) ("The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *See also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007) (predictable variation bars patentability) and *In re O'Farrell,* 853 F.2d 894, 903-04 (Fed. Cir. 1988) (requiring reasonable expectation of success). As evident from the Relkin Declaration, a person of ordinary skill in the art would have neither the required rationale/motivation for combining Becker with Audia and Johnson-Wood or Becker with Mak, nor the required reasonable expectation of success. For at least these reasons, the obviousness rejections should be withdrawn.

As set out in the Relkin Declaration, Becker is directly solely to conformation specific antibodies, with the "vast majority" of Becker being directed to β-amyloid peptide having a predominantly β-sheet conformation. Relkin Declaration at paragraphs 13-16. In view of Becker's singular focus on conformation specific-antibodies and the failure to mention any other type of antibody, Dr. Relkin reports that a person of ordinary skill in the art in April 1997 "would have understood that when Becker refers to 'antibodies of the invention' it refers to conformation specific anti-β amyloid peptide antibodies" and that, when construed properly in this context, Becker's teaching that "antibodies of the present invention" can be used for the treatment of Alzheimer's disease is properly understood to teach that conformation specific antibodies to β amyloid can be used to treat Alzheimer's disease. Relkin Declaration at paragraph 17. As reported in the Relkin Declaration, a person of ordinary skill in the art in 1997 would not have considered the 3D6 antibody described in Audia and Johnson-Wood nor a modification of the anti-40 described in Mak to be a candidate for use in Becker's methods. Relkin Declaration at paragraphs 19-22 and 30-32.

With respect to the 3D6 antibody, Dr. Relkin points out that the 3D6 antibody is directed to a linear epitope at the amino terminus of Aβ1-40 and that in 1997 such an antibody would have been considered "very unlikely" to be a conformation specific antibody and, conversely, would have been likely to be directed against a denatured epitope. Relkin Declaration at paragraphs 19-20. Based on his experience in the field, Dr. Relkin found it "highly unlikely" that a person of ordinary skill in the art in April 1997 would have considered the 3D6 antibody to have been among the conformation specific antibodies contemplated by Becker. Relkin Declaration at paragraph 20.

Dr. Relkin further explains that in April 1997 it was known that anti-β amyloid antibodies selected on different principles and properties would have been expected to have different biological effects and side effects. Relkin Declaration at paragraph 21. In April 1997, it was known, for example, that the Aβ disaggregation activity of monoclonal antibodies varied from antibody to antibody. *Id.* Dr. Relkin reports that a person of ordinary skill in the art in April 1997 would have understood that conformation specific antibodies (as referred to in Becker) and short, linear-epitope antibodies (such as 3D6) are "substantively different" and

based on "such different principles" that they "would very likely have different therapeutic effects" and "may have different side effects." *Id.* Based on his experience and knowledge of the field in 1997, Dr. Relkin reports that differences in the respective binding principles of the conformation specific antibody and the 3D6 antibody would have been "highly relevant" in April 1997 and "highly indicative" that the 3D6 antibody should not be used in place of a conformation specific antibody. *Id.*

In short, Dr. Relkin reports that a person of ordinary skill in the art in April 1997 would have considered conformation specificity to be a "threshold selection criterion" for antibodies that were to be used in Becker's methods and that in April 1997 the 3D6 antibody would not have been considered to be a candidate for Becker's methods because it would have been recognized to fail such a "threshold selection criterion." Relkin Declaration at paragraph 22. Based on his knowledge and experience, Dr. Relkin concludes "a person of ordinary skill in the art in April 1997 would therefore not have been motivated to use the 3D6 antibody in any method disclosed in Becker." *Id.*

With respect to Mak, the Relkin Declaration sets out that a person of ordinary skill in the art in April 1997 would have concluded that Mak's polyclonal "anti-40" antibody was not a conformation specific antibody and that neither would a monoclonal antibody with the same specificity as the anti-40 antibody have been likely to be a conformation specific antibody. Relkin Declaration at paragraph 30. Dr. Relkin reports that, for essentially the same reasons elaborated upon above in connection with the rejections based on Becker, Audia and Johnson-Wood, a person of ordinary skill in the art in April 1997 would have not combined Becker with Mak because (1) Becker's teachings would have been understood to be restricted to conformation specific antibodies; (2) there are "fundamental distinctions" between conformation specific antibodies and linear-epitope antibodies; and (3) Becker does not teach the use of "any" anti-β amyloid antibody. Relkin Declaration at paragraph 32. For at least these reasons, a person of ordinary skill in the art in April 1997 would not have been motivated to combine Becker with Mak to arrive at the claimed invention. The rejection based on Becker and Mak should thus be withdrawn.

In summary, the Relkin Declaration reports that a person of ordinary skill in the art in April 1997 would not combine Becker with Audia and Johnson-Wood or Becker with Mak. First the skilled person would have understood that conformational specificity is a "threshold" for antibodies to be used in Becker's methods and the skilled person would have understood that neither the 3D6 antibody nor a monoclonal antibody with the specificity of the anti-40 antibody would have been a conformation specific antibody. A skilled person would therefore not have been motivated to combine Becker with Audia, Johnson-Wood or Mak. Second, in view of the different principles used to select conformation specific antibodies versus epitope-specific antibodies and the unpredictability of biological activity among anti-Aβ antibodies that recognize different epitopes, there was no reasonable expectation that the 3D6 antibody or a monoclonal antibody with the activity of the anti-40 antibody could be used successfully in Mak's methods. In the absence of a motivation to combine the prior art and the lack of a reasonable expectation of success, the rejections over Becker and Audia and Johnson-Wood and Becker and Mak should be withdrawn.

Failure to Ascertain the Scope and Content of the Prior Art

The rejections should also be withdrawn because, in setting out the rejections, the Examiner failed to properly ascertain the scope and content of the prior art. This failure, in turn, lead the Examiner to use an unsupported rationale as the basis for combining the prior art to arrive at the claimed invention.

To support a finding of obviousness, the Examiner must make basic factual enquires as to (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; and (3) the level of ordinary skill in the pertinent art. *KSR* 550 U.S. at 406, *quoting Graham v. John Deere Co.,* 383 U.S. 1, 17-18 (1966). *See also* MPEP 2141 ("Factual findings made by Office personnel are the necessary underpinnings to establish obviousness.") Here, the Relkin Declaration reports that the instant rejections, as laid out by the Examiner, are "based on certain mistaken facts, assumptions, and/or conclusions" and "misinterpretation" of the prior art. Relkin Declaration at paragraphs 23 and 33.

The Relkin Declaration thus sets out reasons the Examiner is mistaken to conclude that Becker teaches "any" Aβ antibody can be used to treat Alzheimer's disease. Dr. Relkin reiterates that Becker is directed exclusively to conformation specific antibodies, whereas in April 1997 "most all anti-β amyloid antibodies were characterized on the basis of their binding to linear epitopes within the primary sequence of Aβ, not by recognition of specific higher order conformations." Relkin Declaration at paragraph 24. As reported in the Relkin Declaration, anti-peptide antibodies to Aβ were well known when Becker applied for a patent and "Becker could have easily indicated" that such linear-epitope antibodies were part of Becker's invention. *Id.* Becker chose not to disclose linear-epitope antibodies, however, and limited his disclosure to conformation specific antibodies. *Id.* According to Dr. Relkin, "[t]he Examiner's position that Becker teaches 'any' Aβ antibody can be used to treat Alzheimer's disease ignores this important distinction and does not reflect the way a person of ordinary skill in the art in April 1997 would have interpreted Becker's teachings." *Id.* Moreover, the Relkin Declaration reports that proteins or peptides can assume a configuration that lacks any identifiable secondary structure. Relkin Declaration at paragraph 25. The Examiner is incorrect to assert that the β-sheet, α-helix, and random coil conformations disclosed in Becker constitute the "full complement of conformations available to the β-amyloid peptide." *Id.* The Examiner's assertion that Becker teaches that "any" Aβ antibody can be used to treat Alzheimer's disease is thus incorrect. *Id.* The Examiner's assertion that Becker teaches "any" Aβ antibody can be used to treat Alzheimer's disease is critical to all pending rejections. The mistaken assertion is thus grounds for withdrawal of all rejections.

The Relkin Declaration sets out additional asserted "facts" relied upon in making the rejection that are not supported by the prior art of record. Dr. Relkin points out that there is no support for the Examiner's assertion that conformation specific antibodies specific to Aβ in an α-helical conformation would necessarily prevent β-sheet formation and thus prevent β amyloid neurotoxicity. Relkin Declaration at paragraph 26. With respect to the 3D6 antibody, the Relkin Declaration reports that there is insufficient information in Johnson-Wood to support the Examiner's assertion that Johnson-Wood teaches the 3D6 antibody binds to amyloid plaques

"very well" and with "superior ability." Relkin Declaration at paragraph 28. These asserted "facts" relied upon by the Examiner in finding a motivation to substitute the 3D6 antibody in Becker's methods are thus not correct. These are additional reasons the rejections based on Becker, Audia and Johnson-Wood should be removed.

Moreover, as set out in the Relkin Declaration, the observation that the 3D6 antibody was a free end-specific antibody would not have motivated a person of ordinary skill in the art in April 1997 to use the 3D6 antibody in Becker's methods because, notwithstanding such free end-specificity, the 3D6 antibody fails Becker's threshold requirement that antibodies be conformation specific antibodies. Relkin Declaration at paragraph 27. As noted by Dr. Relkin, the Examiner's stated rationale for the motivation for using a free-end specific antibody is effectively lifted from the instant specification. In the absence of support for this rationale in the Office Action, it is apparent that the Examiner has impermissibly used the inventor's own disclosure and hindsight to arrive at this stated rationale for using the 3D6 antibody in Becker's methods. Such hindsight has been condemned by the courts. In re Dow Chem. Co., 837 F.2d 469, 473 (Fed. Cir. 1983) ("There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure."); see also KSR 550 U.S. at 421 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning."

The Relkin Declaration further reports that the Examiner's stated rationale for combining Becker and Mak is based on misinterpretation of Mak and taking Mak out of context. Dr. Relkin reports that, when fairly interpreted, a person of ordinary skill in the art in April 1997 would have understood that Mak teaches that Aβ1-40 is a minor component of plaques and is not the likely pathogenic agent in Alzheimer's disease and that Aβ1-40 is the major Aβ species in normal CSF. Relkin Declaration at paragraph 34. The Examiner is thus "simply wrong" to assert that Mak teaches Aβ1-40 is the major Aβ species in Alzheimer's disease. Mak Declaration at paragraph 35. Moreover, Dr. Relkin reports, Tamaoka et al., *J. Neurol. Sci.,* 1997, 148:41-45, reported no change in the levels of Aβ1-40 in the CSF of Alzheimer's disease patients, compared to control groups, further indicating that in April 1997, Aβ1-40 would not have been considered to be the predominant Aβ component in Alzheimer's disease. Relkin

Declaration at paragraph 36. In relying upon the assertion that Aβ1-40 "is the major species present in CSF of Alzheimer's patients" to make the instant rejection, the Examiner does not fairly discern the scope and content of the prior art. *Id.*

Nor does the Examiner's statement that "Mak suggests the C-terminus of Aβ may be an important variable in Alzheimer's disease pathology" accurately reflect the scope and content of the prior art. As reported in the Relkin Declaration, the Examiner's statement is "completely stripped of its context." Relkin Declaration at paragraph 37. When properly considered, Mak indicates that the C-terminus of Aβ is "an important variable in Alzheimer's disease pathology" because Aβ1-42 is exhibits pathogenic properties that Aβ1-40 is much less prone to exhibit. *Id.* This does not indicate that Aβ1-40 is the likely pathogenic agent in Alzheimer's disease (*id.*) and thus does not support the Examiner's assertion that Mak provides a motivation to use an antibody specific to the C-terminus of Aβ1-40 in Becker's methods.

In short, as reported in the Relkin Declaration, the Examiner failed to properly ascertain the scope and content of the prior art. The Examiner has thus failed to provide "the necessary underpinnings to establish obviousness." MPEP 2141. In view of the Examiner's flawed factual findings concerning the prior art, the Examiner has also failed to provide a legitimate rationale to combine and modify the prior art to arrive at the claimed invention. For these additional reasons, the instant rejections should be withdrawn.

NOT Obvious to Try

The evidence presented in the Relkin Declaration also demonstrates that it would not have been obvious to try the 3D6 antibody or a modified version of the anti-40 antibody in Becker's methods. The Supreme Court in *KSR* reiterated that "obvious to try" may be appropriate where "there are a finite number of identified, predictable solutions" that "leads to the anticipated success." *KSR International Co. v. Teleflex Inc.,* 550 U.S. 398, 421 (2007). Here, obvious to try fails on requirements.

With respect to a finite number of identified, predictable solutions, the Relkin Declaration reports that many anti-Aβ antibodies had been developed by 1994 (i.e., over 2 years before April 1997). Relkin Declaration at paragraph 24. The only rationale provided by the

Examiner as to why it would have been obvious to use a free end-specific antibody is the circular reasoning that such an antibody would recognize Aβ but not closely related molecules such as APP. As pointed out by Dr. Relkin, however, the prior art fails to support provide any advantage of this property in a therapeutic antibody. The Examiner has therefore failed to provide a legitimate rationale for choosing a free end-specific antibody from among all Aβ antibodies that were known in April 1997. An obvious to try rationale thus fails because the 3D6 antibody and the anti-40 antibody were not chosen from a finite number of possibilities.

The obvious to try rationale also fails because the use of the 3D6 or anti-40 antibody would not have been a "predictable" solution leading to an "anticipated success" of treating Alzheimer's disease. In its Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex ("Examination Guidelines Update"), the PTO noted, "[t]he Federal Circuit cautioned that an obviousness to try rationale must always be undertaken in the context of the subject matter in question, 'including the character, its state of advance, the nature of the known choices, the specificity or generality of the prior art, and the predictability of results in the area of interest." Examination Guidelines Update, 75 Fed. Reg. Vol., No. 169, 53643, 53653, September 1, 2010, *citing Abbott Labs. v. Sandoz, Inc.,* 544 F.3d 1341, 1352 (Fed. Cir. 2008). The Examination Guidelines Update further notes that courts have applied KSR "in a manner that places particular emphasis on predictability and the reasonable expectations of those of ordinary skill in the art" *(id.)* and cautions, "Office personnel should recognize that even when only a small number of possible choices exist, the obvious to try line of reasoning is not appropriate when, upon consideration of all of the evidence, the outcome would not have been reasonably predictable and the inventor would not have had a reasonable expectation of success" (*id.* at 53656, emphasis added to original).

In a post-KSR decision, the Federal Circuit confirmed an obvious to try standard is "appropriate where the prior art 'contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.'" *In re Kubin,* 561 F.3d 1351, 1360 (Fed. Cir. 2009), *quoting In re O'Farrell*, 853 F.2d at 903. Here, the prior art failed to provide any example or detailed guidance for using antibody therapy to treat Alzheimer's disease. The prior

art thus failed to provide a "detailed enabling methodology" for treating Alzheimer's disease. The Relkin Declaration, moreover, makes it abundantly clear that a person of ordinary skill in the art in April 1997 would have considered the therapeutic efficacy of antibodies for treating Alzheimer's disease to be unpredictable, from antibody to antibody, depending upon factors such as the principle by which an antibody is selected and the particular epitope recognized by an antibody. *See* Relkin Declaration at paragraph 19. In short, one of ordinary skill in the art in April 1997 would not have considered the use of the 3D6 antibody or a variation of the anti-40 antibody to have been "predictable solutions" that would "[lead to an] anticipated success." An obvious to try rationale thus also fails because in April 1997 there was not a reasonable expectation of success in using the 3D6 antibody or the anti-40 antibody to treat Alzheimer's disease.

Conclusion

For all of the reasons set out above, the claims are not obvious over Becker in view of Audia and Johnson-Wood or Becker in view of Mak. Reconsideration of the claims and withdrawal of all rejections under 35 U.S.C. 103 is requested.

III. Conclusion

This application is in condition for allowance, which is earnestly solicited.

Respectfully submitted,

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